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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Martin et al. Confirmation No. 7329  
Serial No. 10/601,757 Group Art Unit: 1625  
Filed 06/24/2003 Examiner: Owens  
For **"SULFONAMIDE CANNABINOID AGONISTS AND ANTAGONISTS"**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

## DECLARATION UNDER 37 C.F.R. 1.131 and/or 1.132

Sir:

Billy R. Martin declares as follows:

1. I am an inventor on the above-referenced patent application which is for an invention for which an Invention Disclosure was prepared for my signature, which I signed March 26, 2002, and submitted to Virginia Commonwealth University (VCU)'s Technology Transfer office. A copy of the Invention Disclosure is attached hereto.

2. I hold the positions of Louis and Ruth Harris Professor, and Chair of Pharmacology and Toxicology at Virginia Commonwealth University.

3. As reported in paragraph 12 of the Invention Disclosure, at the time my co-inventors and I were submitting an abstract for presentation at a scientific meeting July 12-14, 2002, which was the ICRS 12<sup>th</sup> Annual Symposium on the Cannabinoids, at Pacific Grove, California. The abstract titled "Agonists and Silent Antagonists in a series of Cannabinoid Sulfonamides" that the Examiner has provided and that is by Billy R. Martin et al., is the abstract to which I was referring in my Invention Disclosure. In my academic field, it is customary to share and disseminate information about one's inventions and discoveries with non-inventors in an academic setting. Adding others who are non-inventors on an abstract is one way of doing so. Lesley A. Stevenson, Christopher S. Breivogel, W. Williams and Anu Mahadcvan were named on the July 2002 abstract and derived their knowledge of the invention documented in my March 2002 Invention Disclosure through Razdan, Pertwee and/or me.

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4. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application and any patent issuing thereon.

Date 11/6/06

Billy R. Martin  
Billy R. Martin

Name

03/26/02

**Confidential Information****Virginia Commonwealth University****Invention Disclosure**

Inventor(s)	<u>Martin Hal</u>
VCU Invention No.	<u>02-20</u>
Original	
Modification #	
Date Received	<u>MAR 28 2002</u>

**RECEIVED**  
**TECHNOLOGY TRANSFER**

Inventions may lead to new products and processes, and may bring research support, as well as royalties, to the inventor and the University. This VCU Invention Disclosure Form is intended to describe succinctly, but completely the invention, its use, and the inventor's ideas for its commercialization.

Please use this form both for an initial disclosure and for any supplementary or changed information to a previously filed disclosure. Please respond to all the questions. For a supplement/change, please complete only the affected questions. All inventors should sign each disclosure form submitted. Use supplementary sheets when needed.

Each invention report will be reviewed to determine VCU's plan of action. The inventor will probably be contacted for more information. This process will take from one to six months, depending on the complexity of the situation.

**The Inventions**

1. Title of the Invention: Sulfonamide cannabinoid agonists and antagonists

2. Give a concise description of the invention, which should be sufficiently detailed to enable one skilled in the art to understand and reproduce the invention, and should include construction, principles involved, details of operation and alternative methods of construction or operation. Attach drawings, photos, manuscripts, and sketches that help describe the invention. Is it a new process, composition of matter, a device or one or more new products? Is it an improvement to, or a new use of an existing product or process?

We have discovered that introduction of a sulfonamide into the side chain of cannabinoids can result in either potent agonists or antagonists.

3. What is novel or unusual about this invention? How does it differ from present technology? What are its advantages?

The introduction of a sulfonamide with a methyl substituent resulted in antagonism which is highly unusual. In addition, this antagonist lacks inverse agonist properties that other cannabinoid antagonists possess.

4. What is the closest technology currently available, upon which this invention improves?

The closest technology is SR 141716A which is a pyrazole and structurally distinct from the present compound.

5. What disadvantages does this invention have? How can they be overcome?

6. What uses do you foresee for the invention, both now and in the future?

It is not yet clear whether the agonists offer any advantages over existing cannabinoids agonists. The agonists have potential as analgesics, appetite stimulants, anticonvulsants, treatment of multiple sclerosis and treating nausea and vomiting. The antagonists have the advantage of lacking inverse agonist properties. They have potential for treating memory deficits and obesity. The antagonist should be a valuable research tool.

Name

03/26/02

7. Has any commercial interest been shown in the invention? Please give company and individual's names, and addresses if available.

NO

8. What other companies or industry groups might be interested in this invention, and why?

BTG, Organon and GW Pharmaceuticals, plc for the therapeutic reasons discussed above. Companies such as Tocris might want to add it to their chemical catalog, however, this strategy should be our last resort.

9. Please comment on any preferences or ideas you have for a good way to commercialize this invention.

10. What additional work is needed to bring the invention to a licensable state? Please estimate times and cost.

The pharmacological properties of these compounds need to be established in a wide range of in vivo and in vitro models.

11. Has the invention been described in a "publication" (journal articles, abstracts, news stories, and talks)? Please provide details including dates and copies of written material.

No.

12. Do you plan to publish within the next 6 months? Please provide approximate date and any abstract, manuscript etc. available?

We are submitting an abstract for presentation at a scientific meeting July 12-14.

13. Dates of record, demonstrable from lab notebooks, correspondence etc.:

- Earliest conception: 6/28/91
- First disclosure date: 10/29/96
- First disclosure to whom: NIH grant application
- First reduction to practice: 2/8/00 Organix notebook no. 149, page 191, 197. Synthesis of O-1991.

14. Please list all sources of support contributing to this invention (give account numbers):

- University funds (Dept. etc):
- Sponsored funds: NIDA grants DA-05488 and DA-03672.

• The Inventor(s) (Complete as many as needed).

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See next page

**Administrative Certification**

16. (To be completed by Department Chairman, Program Director, or other Supervisor before submitting document to the Office of Technology Transfer). I have reviewed the information provided above, with particular reference to the source(s) of funds contributing to the invention. To the best of my knowledge, I believe the above statement to be accurate.

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26/03/2002 11:17 44-122 7019

BIOMED SCI UNIV A

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333<sup>2/10</sup>

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Date: 26th March 2002

**Administrative Certification**

16. This document has been reviewed by Department Chairman, Program Director, or other Supervisor before submitting documents to the Office of Technology Transfer. I have reviewed the information provided above, with particular reference to the source(s) of funds contributing to the invention. To the best of my knowledge, I believe the above statement to be accurate.

Name

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Signature: \_\_\_\_\_

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03/26/02

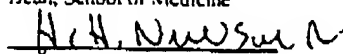
**Administrative Certification**

16. (To be completed by Department Chairman, Program Director, or other Supervisor before submitting document to the Office of Technology Transfer). I have reviewed the information provided above, with particular reference to the source(s) of funds contributing to the invention. To the best of my knowledge, I believe the above statement to be accurate.

Name: H.H. Newsome, Jr., MD

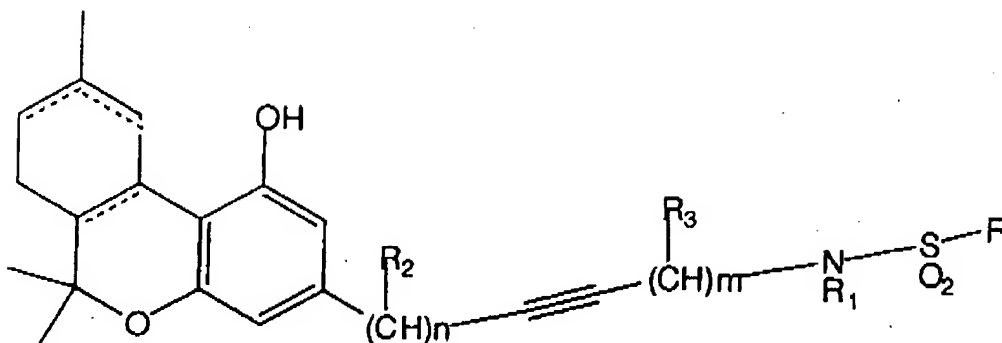
Title: Dean, School of Medicine

Signature:



Date:

2002

 $n = 0-7$  $m = 0-7$  $n$  and  $m$  can be the same or different $R_1$  = H, alkyl, phenyl, substituted phenyl $R_2$  and  $R_3$  are any of H, alkyl $R$  = alkyl ( $C_1$  to  $C_7$ ), cycloalkyl, phenyl, hydroxy, alkyl hydroxy, substituted phenyl, and  $CH_2X$  where  $X$  = H, Cl, Br, I, F

### Development of sulfonamides as agonists and "silent" antagonists.

It has been well established that the alkyl side chain of tetrahydrocannabinoids is critical for this class of compounds to produce their agonist effects. In addition, there have been numerous alterations in the side chain as a means of further exploring its role in cannabinoid action.

In an effort to extend the structural requirements for agonist effects, we incorporated a sulfonamide moiety into the side chain. Moreover, a sulfonamide moiety has been known to impart antagonistic activity in some classes of compounds. Known cannabinoid antagonists also elicit inverse agonism. Therefore, there is a need to develop a cannabinoid antagonist lacking inverse agonist properties, or so called "silent" antagonists.

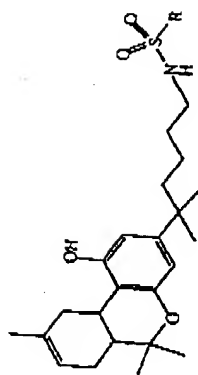
Incorporation of an ethyl and phenyl substituted sulfonamide into the terminal position of a dimethylphenyl side chain of  $\Delta^9$ -THC resulted in analogs O-2113 and O-2048. Both compounds exhibited high affinity for both cannabinoid receptor subtypes (Fig. 1). Additionally, both compounds were potent cannabinoid agonists as determined in the mouse tetrad test. The ED<sub>50</sub>'s (mg/kg) for producing sedation, analgesia and hypothermia following i.v. administration in mice are presented in Fig. 1. However, changing the side chain to a hex-2-yne with a sulfonamide substitution at the terminal carbon resulted in a separation of pharmacological properties. An ethyl and butyl substituent on the sulfonamide resulted in analogs O-1991 and O-1993 that had moderate affinity for the CB<sub>1</sub> receptor and moderate to low pharmacological agonist potency in the mouse tetrad tests (Fig. 2). However, O-2050 had a methyl substituent on the sulfonamide and had high affinity for both CB<sub>1</sub> and CB<sub>2</sub> receptors. In contrast to all of the sulfonamide analogs, it was only weakly active in producing sedation and failed to produce either analgesia or hypothermia at doses up to 30 mg/kg.

The above properties of O-2050 are indicative of an antagonist. Therefore, we evaluated O-2050 *in vitro* for its ability to block the agonist effects of CP 55,940, a highly efficacious cannabinoid, in the GTP $\gamma$ S binding assay in rat brain tissue. This assay is an *in vitro* functional measure of CB<sub>1</sub> receptor activation. As seen in Fig. 3, O-2050 was effective in antagonizing the actions of CP 55,940-induced activation of GTP $\gamma$ S binding. In order to determine whether O-2050 had inverse agonist properties, it was examined alone in the GTP $\gamma$ S binding assay. The results in Fig. 4 demonstrate that O-2050 failed to produce negative stimulation and therefore lacks inverse agonist properties in brain. We extended these observations by examining O-2050 in the mouse vas deferens, a smooth muscle preparation that is regulated by the cannabinoid system. Another cannabinoid agonist, WIN 55,212, was used to demonstrate inhibition of electrically induced contractions of the mouse vas deferens (open circles in Fig. 5). In the presence of increasing concentrations of O-2050, the actions of WIN 55,212 were antagonized increasingly. Thus, O-2050 was found to be a highly potent antagonist with a K<sub>B</sub> value of 1.0 nM. Finally, we demonstrated that O-2050 lacks inverse agonism in the mouse vas deferens as shown in Fig. 6.



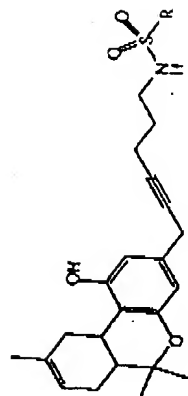
The results of these series of studies are summarized in Fig. 7. Sulfonamides analogs of THC can either be agonists or antagonists. More importantly, O-2050 is a highly potent antagonist that lacks inverse agonist properties.

Fig. 1. Saturated Side Chain  
Sulfonamides



O#	R	CB1 KD	CB2 KD	Sedation	Analgesia	Temp.
2113	Ethyl	1.7±0.3	0.08±0.02	0.4	0.3	1.4
2048	Phenyl	4.1±0.4	6.9±1.3	0.3	2.8	5.6

Fig. 2. Unsaturated Side Chain  
Sulfonamides



O#	R	CB1 KD	CB2 KD	Sedation	Analgesia	Temp.
2050	Methyl	2.5±0.4	0.2±0.06	4.3	>30	>30
1991	Ethyl	30±13	1.4±0.2	1.7	0.9	0.8
1993	Butyl	70±10	86±7	7.6	14	12

Fig. 3. O-2050 Blocks CP 55,940  
Stimulation of GTPγS binding

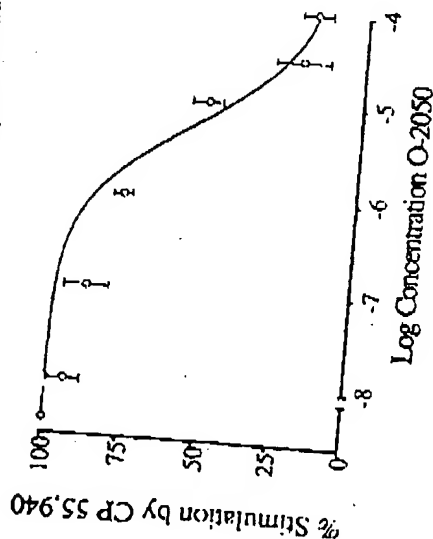


Fig. 4. O-2040 Lacks Inverse Agonism in  
GTPγS Binding in Rat Brain Membranes

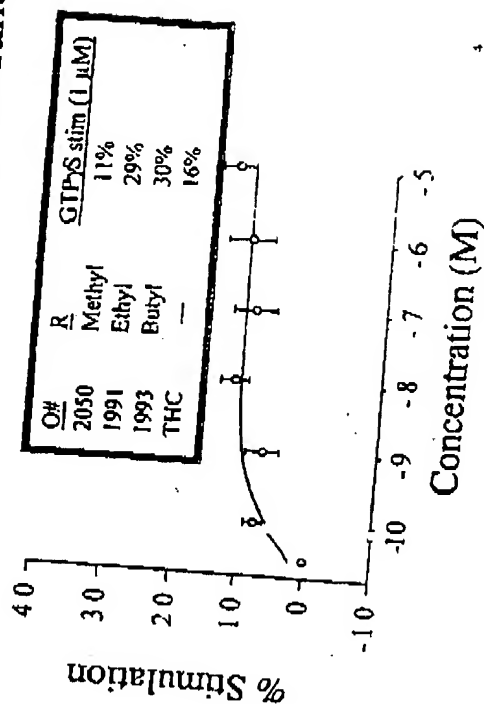


Fig. 5. O-2050 Antagonism of WIN 55,212-2 in Mouse Vas Deferens

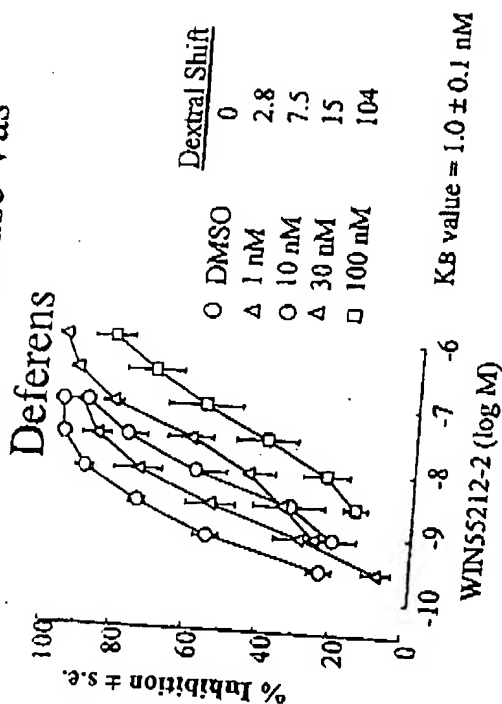


Fig. 6. O-2050 Lacks Inverse Agonism in Mouse Vas Deferens

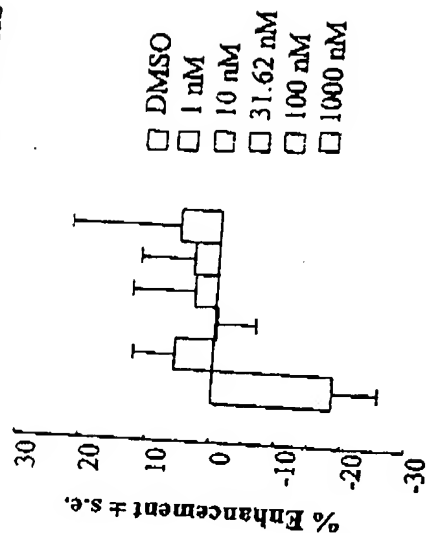


Fig. 7. Summary

- O2113 and O-2048 are cannabinoid agonists
- O-1991 and O-1993 are cannabinoid agonists
- O-2050 has high CB1 receptor affinity without agonists effects in vivo and in vitro
- O-2050 failed to antagonize  $\Delta^9$ -THC in vivo
- O-2050 is an antagonist in functional assays and in MVD
- O-2050 lacks inverse agonist effects
- O-2050 serves as a template for further exploring structural requirements for antagonism/inverse agonism

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November 8, 2006

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Number of Pages (including this cover sheet): 12

**Comments:**

Attached is an additional Declaration Under 37 CFR §1.131 with date-stamped invention disclosure.